UNITED STATES PATENT AND TRADEMARK OFFICE

cll

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/779,731	02/18/2004	Marc G. Achen	029065.44660D2	2156

23911 7590 10/11/2005

CROWELL & MORING LLP
INTELLECTUAL PROPERTY GROUP
P.O. BOX 14300
WASHINGTON, DC 20044-4300

EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 10/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/779,731	ACHEN ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 46-52 are pending.

2. In view of the amendment filed 7/25/05, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 47 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the 2F8 (ATCC No. PTA-3653), 4A5 (ATCC No. HB-12698), 4E10 (ATCC No. PTA-3652), and 5F12 (ATCC No. PTA-3651) antibodies are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Applicants' arguments filed 7/25/05 have been fully considered but are not found persuasive.

Applicants' position is that attention is directed to the paragraph added to page 19, line 15 of the specification by the First Preliminary Amendment filed February 18, 2004 which includes complete, updated deposit information for the deposited antibodies. Any basis for this rejection is believed to have been obviated by this amendatory matter.

In response, although the deposit information for the deposited antibodies under Budapest Treaty in the specification has been updated by the First Preliminary Amendment filed February 18, 2004, the statement satisfying that all restrictions imposed by the depositor on the availability

to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications has not been filed.

5. Claims 46 and 48-52 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method for imaging of lymphatic vasculature in tissue comprising the steps of contacting the sample with an antibody or a labeled antibody or binding fragment thereof selected from the group consisting of monoclonal antibody 2F8 (ATCC No. PTA-3653), 4A5 (ATCC No. PTA-12698), 4E10 (ATCC No. PTA-3652) and 5F12 (ATCC No. PTA-3651) which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, **does not** reasonably provide enablement for a method for imaging of lymphatic vasculature in tissue, comprising the step of contacting the tissue with *any* antibody which interferes with binding of any VEGF-D to any VEGF receptor-3, and detecting the occurrence of binding of said antibody as set forth in claims 46 and 48-52. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only monoclonal antibodies with laboratory designation as MAb 2F8, MAb 4A5, MAb 4E10 and MAb 5F12 for a method of detecting VEGF-D in biological sample.

Other than the specific antibodies mentioned above for a method of detecting VEGF-D in a sample, there is insufficient guidance as to the chemical structures of immunogen used by applicants and the binding specificity of all antibodies which interfere with binding of all VEGF-D to its VEGF receptor-3.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See

abstract, in particular). Given the indefinite number of undisclosed immunogenic determinant to which the antibody binds, there is insufficient guidance and working example in the specification as-filed on binding specificity, the epitope to which the antibody binds to direct a person of skill in the art in how to make said antibody.

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimentional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. Without the specific amino acid residues of the immunogen, it is unpredictable which antibody in the claimed method generated from any fragment will have the same antibody binding specificity as an antibody generated from the full-length polypeptide, in turn, said antibody will be effectively interferes with the binding of VEGF-D to its receptors such as VEGF receptor-2 and VEGF receptor-3.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/25/05 have been fully considered but are not found persuasive.

Applicants' position is that the sequence of VEGF-D is known (see e.g. WO 98/07832, of record). It is unquestionably within the skill of the art to raise monoclonal antibody to this known protein. Indeed, it can be done analogously to the procedure used to obtain the specifically disclosed antibodies.

In response, the binding specificity of the antibody in the claimed method is ambiguous. The antibody in claim 46 as written could be antibody to VEGF-D or VEGF receptor-3. Claim 46 does not recite the method for imaging of lymphatic vasculature in tissue using antibody or F(ab')2, F(ab'), F(ab) fragment or chimeric antibody thereof that binds specifically to VEGF-D

comprising SEQ ID NO: 1 wherein the antibody interferes with binding of VEGF-D to a VEGF receptor-3, and detecting the occurrence of said binding.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 46, and 48-51 stand rejected under 35 U.S.C. 102(a) as being anticipated by WO 98/07832 publication (Feb 26, 1998; PTO 1449).

The WO 98/07832 publication teaches a method for imaging lymphatic vasculature in tissue comprising the step of contacting the tissue with an antibody such as monoclonal antibody and polyclonal antibodies that bind specifically to human or mouse VEGF-D (see page 10, lines 10-17, in particular). The reference VEGF-D antibodies inherently interfere with binding of VEGF-D to its receptor such as VEGF receptor-3 (see page 38, line 34, in particular). The reference antibody such as monoclonal and polyclonal antibody is labeled covalently or noncovalently with a detectable label such as enzyme, or fluorimetric label such as biotin/avidin, supermangetic, paramagnetic, electron dense, ecogenic or radioactive agent (see page 10, lines 15-20, in particular), horseradish peroxidase (HRP) (see page 36, line 27, in particular). Therefore the antibody in the claimed method appears to be the same as that of the prior art antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 7/25/05 have been fully considered but are not found persuasive.

Applicants' position is that the cited document does not describe the claimed invention. The cited document merely notes that antibodies to VEGF-D could be labeled with a detectable label and used for imaging. Conspicuously absent is any of antibodies which interfere with binding of VEGF-D to VEGF receptor-3.

In response, Claim 46 does not recite the method for imaging of lymphatic vasculature in tissue using antibody or F(ab')2, F(ab'), F(ab) fragment or chimeric antibody thereof that binds

specifically to VEGF-D comprising SEQ ID NO: 1 wherein the antibody interferes with binding of VEGF-D to a VEGF receptor-3, and detecting the occurrence of said binding.

In contrast to applicant's assertion that the cited document does not describe the claimed invention, the WO 98/07832 publication teaches a method for imaging lymphatic vasculature in tissue comprising the step of contacting the tissue with an antibody such as monoclonal antibody and polyclonal antibodies that bind specifically to human or mouse VEGF-D (see page 10, lines 10-17, in particular). The reference VEGF-D antibodies *inherently* interfere with binding of VEGF-D to its receptor such as VEGF receptor-3 (see page 38, line 34, in particular). Given the binding specificity of the antibody in the claimed method is ambiguous at best, the reference teachings appear to teach the claimed invention.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 46, 48-50 and 52 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/07832 publication (Feb 26, 1998; PTO 1449) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, page 319-329).

The teachings of the WO 98/07832 publication have been discussed supra.

The claimed invention as recited in claims 49 and 50 differs from the teachings of the reference only that the antibody is labeled with a detectable label wherein the detectable label is a radioactive isotope ^{125}I.

The claimed invention as recited in claim 52 differs from the teachings of the reference only that the antibody is labeled with a detectable label wherein the detectable label is a fluorescein-5-isothiocyanate (FITC).

Harlow *et al* teach a method of imaging using any antibody that is labeled with a detectable label such as radioisotope I^{125} (see page 338, in particular). The advantages of radioactive labeling are ease of detection, cheap, and commercially readily available (See page 324, first paragraph, in particular). Harlow *et al* teach antibody labeling with various label such as fluorescein-5-isothiocyanate (FITC) (see page 354, in particular). Harlow *et al* teach the advantages of fluorescein-5-isothiocyanate (FITC) label is its long shelf life, and high resolution immunocytochemistry (see page 321, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to label any antibody binds specific to the VEGF-D as taught by the WO 98/07832 publication with the radioisotope I^{125} label or fluorescein-5-isothiocyanate (FITC) as taught by Harlow *et al* for a method for imaging of lymphatic vasculature in tissue as taught by the WO 98/07832 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach the advantages of radioactive labeling such as I^{125} are ease of detection, cheap, and commercially readily available (See page 324, first paragraph, in particular). The advantage of fluorescein-5-isothiocyanate (FITC) label is its long shelf life, and high resolution immunocytochemistry as taught by Harlow et al (see page 321, in particular).

Applicants' arguments filed 7/25/05 have been fully considered but are not found persuasive.

Applicants' position is that the deficiencies of the primary reference are noted above. Harlow et al. merely discloses antibody labeling with various labels such as fluorescein-5-isothiocyanate (FITC) but does not rectify the failure of the cited WO 98/07832 publication. Thus even if the teaching of the WO publication and Harlow et al were combined and the antibodies of

the WO publication were labeled with FITC, the result would still not correspond to the presently claimed invention.

In response, Claim 46 does not recite the method for imaging of lymphatic vasculature in tissue using antibody or F(ab')2, F(ab'), F(ab) fragment or chimeric antibody thereof that binds specifically to VEGF-D comprising SEQ ID NO: 1 wherein the antibody interferes with binding of VEGF-D to a VEGF receptor-3, and detecting the occurrence of said binding.

In contrast to applicant's assertion that the cited document does not describe the claimed invention, the WO 98/07832 publication teaches a method for imaging lymphatic vasculature in tissue comprising the step of contacting the tissue with an antibody such as monoclonal antibody and polyclonal antibodies that bind specifically to human or mouse VEGF-D (see page 10, lines 10-17, in particular). Given the binding specificity of the antibody in the claimed method is ambiguous at best, the reference teachings appear to teach the claimed invention.

The claimed invention as recited in claims 49 and 50 differs from the teachings of the reference only in that the antibody is labeled with a detectable label wherein the detectable label is a radioactive isotope ^{125}I.

The claimed invention as recited in claim 52 differs from the teachings of the reference only that the antibody is labeled with a detectable label wherein the detectable label is a fluorescein-5-isothiocyanate (FITC).

Harlow *et al* teach a method of imaging using any antibody that is labeled with a detectable label such as radioisotope I^{125} (see page 338, in particular). The advantages of radioactive labeling are ease of detection, cheap, and commercially readily available (See page 324, first paragraph, in particular). Harlow *et al* teach antibody labeling with various label such as fluorescein-5-isothiocyanate (FITC) (see page 354, in particular). Harlow *et al* teach the advantages of fluorescein-5-isothiocyanate (FITC) label is its long shelf life, and high resolution immunocytochemistry (see page 321, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to label any antibody binds specific to the VEGF-D as taught by the WO 98/07832 publication with the radioisotope I^{125} label or fluorescein-5-isothiocyanate (FITC) as taught by Harlow *et al* for a method for imaging of lymphatic vasculature in tissue as taught by the WO 98/07832 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach the advantages of radioactive labeling such as I^{125} are ease of detection, cheap, and commercially readily available (See page 324, first paragraph, in particular). The advantage of fluorescein-5-isothiocyanate (FITC) label is its long shelf life, and high resolution immunocytochemistry as taught by Harlow et al (see page 321, in particular).

11. Claims 46, and 48-52 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 6,342,219 (Filed April 28, 1999; PTO 892) in view of Joukov *et al* (EMBO J 16(13): 3898-3911, 1997; PTO 892).

The '219 patent teaches a method for imaging lymphatic vasculature in tissue comprising the step of contacting the tissue with an antibody such as monoclonal antibody that bind specifically to VEGF such as 2C3 antibody or VEGFR-2 blocking antibody that interferes with the binding of VEGF to VEGFR-2 (see col. 39, lines 10-26, col. 3, line 43-45, in particular). The reference antibody is labeled covalently (see col. 32, lines 10-15, in particular) or non-covalently (in directly) via avidin:biotin (see col. 31, lines 61-62, in particular) with a label such as supermagnetic agent, paramagnetic agent, electron dense agent, radioactive agent or fluorimetric label such as bismuth (III), colbalt (II), iodine 125, rhodamine or fluorescein (see col. 39, lines 20-44, col. 10, lines 24-26, in particular) or enzymatically label such as 3, 3'5,5' tetramethybenzidine (TMB) substrate with peroxidase (see col. 10,35-40, in particular). The '219 patent further teaches a method of making various antibody such as monoclonal, polyclonal antibody to VEGF (see col. 58, line 44 bridging col. 62, in particular).

The claimed invention as recited in claim 46 differs from the teachings of the reference only that the antibody interferes with the binding of VEGF-D to a VEGF receptor 3 instead of VEGF to a VEGFR-2.

Joukov *et al* teaches a method of detecting VEGF in biological sample, comprising the step of contacting the sample with an antibody such as polyclonal antibody 882 which specifically binds to a polypeptide having the amino acid sequence EETIKFAAAHYNTEILK that corresponds to residues 104-120 of VEGF-C, which is identical to a stretch of amino acid residues in the claimed VEGF-D and detecting the occurrence of binding of said antibody (See page 3909, Materials and methods, Generation of VEGF-C antisera and Western blotting, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the VEGF antibody as taught by the '219 patent for the antibody as taught by Joukov *et al* for a method for imaging lymphatic vasculature in tissue as taught by the '219 and Joukov *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do substitute because Joukov *et al* teaches the reference antibody is useful for detecting VEGF in biological sample and the reference inherently interferes with the binding of VEGF-D to its VEGF receptor since the reference antibody 882 which specifically binds to a polypeptide having the amino acid sequence EETIKFAAAHYNTEILK that corresponds to residues 104-120 of VEGF-C, which is identical to a stretch of amino acid residues in the claimed VEGF-D. Therefore the claimed method wherein the claimed antibody binding specificity appears to be the same as that of the prior art antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The '219 patent teaches labeled VEGF antibody is useful for imaging lymphatic vasculature in tissue (see col. 39, lines 10-26, col. 3, line 43-45, in particular).

Applicants' arguments filed 7/25/05 have been fully considered but are not found persuasive.

Applicants' position is that the Thorpe et al. patent is not prior art with respect to the present application as it was not filed until April 28, 2000, which is subsequent to the December 21, 1999 filing date of applicant's grandparent application. No showing has been made that the pertinent disclosure of Thorpe et al. was present in the April 28, 1999 provisional application from which Thorpe claims priority and in the absence of such a showing, Thorpe et al. cannot be attribute the benefit of their provisional application. Jukov et a1. discloses antibodies which bind to VEGF-C, which is a third factor distinct from both VEGF and VEGF-D. Jukov et a1. contains nothing to compensate for the failure of Thorpe et al to disclose or suggest use of labeled antibodies which interfere with binding of VEGF-D to VEGF receptor-a to image the vasculature of the lymphatic system. Thus, even Thorpe et al were prior art, the combined teachings of these references would not make out a proper, prima facie case of obviousness.

In response to applicant's argument that Thorpe et al. patent is not prior art, the Thorpe et al (filed April 28, 1999; PTO 892) is a prior art under 102(e) date because the filing date of the instant claims is deemed to be the filing date of provisional application 60/134,556 filed 5/17/1999 and NOT 60/113,254 which filed 12/21/1998. This is because the provisional application 60/113,254 does not support the claimed limitations "...antibody which interferes with binding of VEGF-D to a **VEGF receptor-3**..." of the instant application.

The '219 patent was cited for teaching a method for imaging lymphatic vasculature in tissue comprising the step of contacting the tissue with an antibody such as monoclonal antibody that bind specifically to VEGF such as 2C3 antibody or VEGFR-2 blocking antibody that interferes with the binding of VEGF to VEGFR-2 (see col. 39, lines 10-26, col. 3, line 43-45, in particular). The reference antibody is labeled covalently (see col. 32, lines 10-15, in particular) or non-covalently (in directly) via avidin:biotin (see col. 31, lines 61-62, in particular) with a label such as supermagnetic agent, paramagnetic agent, electron dense agent, radioactive agent or fluorimetric label such as bismuth (III), colbalt (II), iodine 125, rhodamine or fluorescein (see col. 39, lines 20-44, col. 10, lines 24-26, in particular) or enzymatically label such as 3, 3'5,5' tetramethybenzidine (TMB) substrate with peroxidase (see col. 10,35-40, in particular). The '219 patent further teaches a method of making various antibody such as monoclonal, polyclonal antibody to VEGF (see col. 58, line 44 bridging col. 62, in particular). If the '219 patent teaches the same antibody, this rejection would have been rejected under 35 U.S.C. 102(e) instead of under 35 U.S.C. 103(a).

In response to applicant's assertion that even Thorpe et al were prior art, the combined teachings of these references would not make out a proper, prima facie case of obviousness, in this case the teachings of Thorpe patent pertaining to a method for imaging lymphatic vasculature using labeled antibody that binds to VEGF and the teachings of Joukov *et al* indicating success in detecting VEGF in biological sample using an antibody such as polyclonal antibody 882 which specifically binds to a polypeptide having the amino acid sequence EETIKFAAAHYNTEILK that corresponds to residues 104-120 of VEGF-C, the epitope to which the reference binds has a stretch of amino acid residues that are identical to the claimed VEGF-D would have led one of ordinary skill in the art at the time the invention was made to substitute the antibody in the method as taught by Thope et al for the antibody as taught by Joukov *et al* to arrive at the claimed invention. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established

scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983), see MPEP 2144. As discussed above, the claimed method does not recite the specific antibody.

12. Claim 47 stands free of prior art.

13. No claim is allowed.

14. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

16. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
September 30, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600